Introduction

A field collection site where employees take samples from hunter harvested deer to check for the presence of CWD. (photo courtesy of USDA/APHIS)

Disease Background And Motivation For Report

Chronic wasting disease (CWD) (Williams and Young 1980) is a contagious prion disease of deer (*Odocoileus* spp.) and elk (*Cervus elaphus nelsoni*) (Williams and Young 1993, Williams and Miller 2002), which also has been recently found in moose (*Alces alces*) (Kreeger et al. 2006). Although once thought only to be endemic to northcentral Colorado and southeastern Wyoming, CWD has been detected in free-ranging and captive herds throughout the United States and in two Canadian provinces (Figure I.1). CWD is the only prion disease known to affect free-ranging species (Williams and Miller 2002), and currently is found in is found in a growing number of privately owned captive cervid herds. With more sensitive diagnostic capabilities and increased surveillance for the disease, new foci continue to be documented.

Epidemiological investigations of CWD are in a nascent stage and a thorough understanding of the factors that contribute to the occurrence, the onset of clinical symptoms, and the transmission of CWD remains incomplete. In addition to potentially reducing population growth rates of free-ranging deer and elk populations, which may have an economic impact on wildlife agencies and cascading ecological impacts, CWD has already had an economic impact on commercial cervid operations and may have a deep economic impact if it spreads to livestock or proves to be a threat to human health (Williams and Miller 2002).

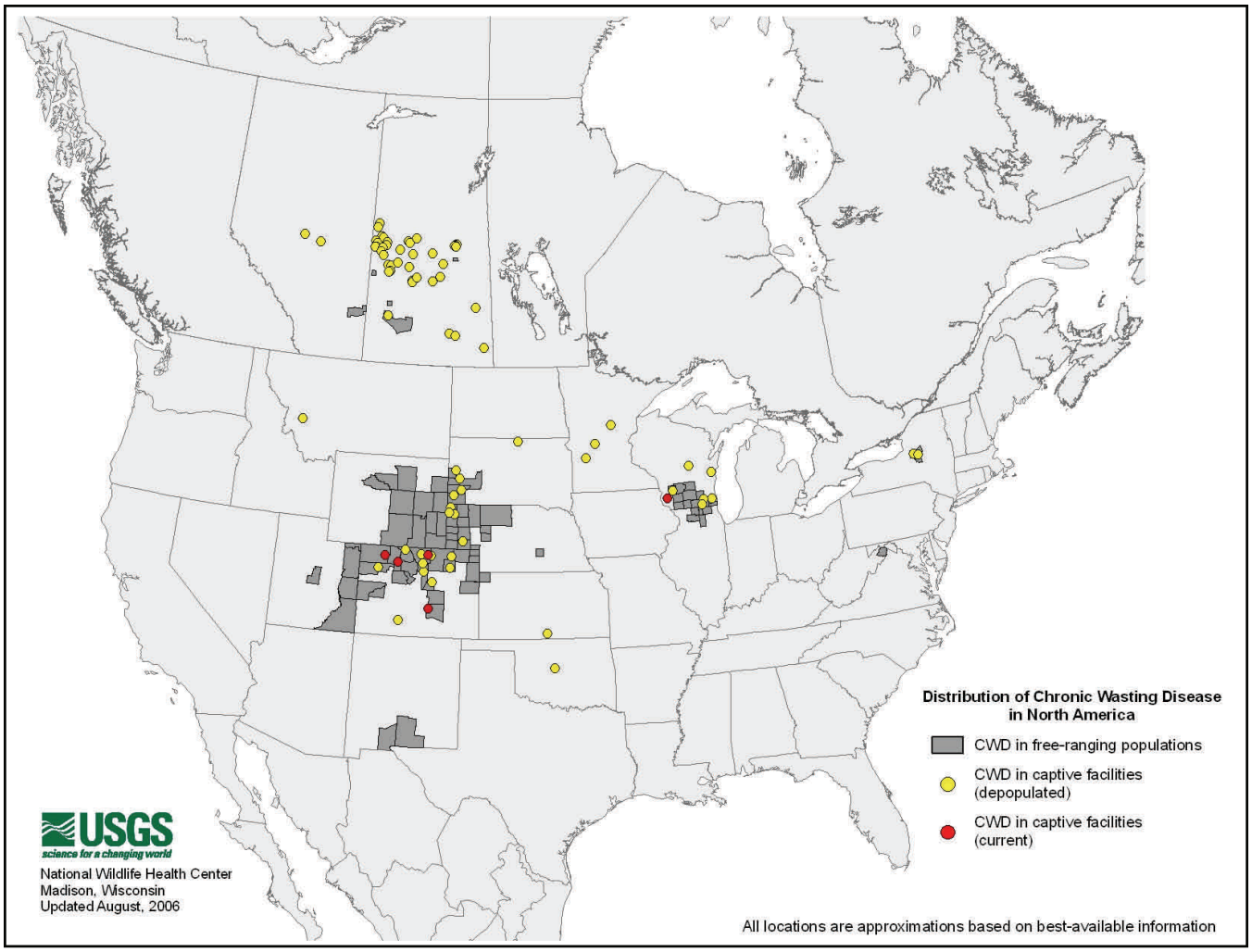


Figure I.1. *Distribution of CWD in North America.*

Given the potential risk and concern about the spread of CWD, there is need to equip ecologists, biologists, and managers with an array of tools to further understand the disease and enhance management efforts. Modeling is a powerful tool that can facilitate formulation and evaluation of potential management strategies, identify risk factors, predict areas at risk, and guide research to enhance mechanistic and biological understanding of CWD transmission and epidemiology.

This e-book is the product of a second workshop promoted by the United States Geological Survey (USGS) to promote cooperation between states for the management of CWD. The first workshop addressed issues surrounding the statistical design and collection of surveillance data for CWD (Samuel et al. 2006). The second workshop, from which this document arose, followed logically from the first workshop and focused on appropriate methods for analysis, interpretation, and use of CWD surveillance and related epidemiology data. Consequently, the emphasis of this e-book is on modeling approaches to describe and gain insight of the spatial epidemiology of CWD.

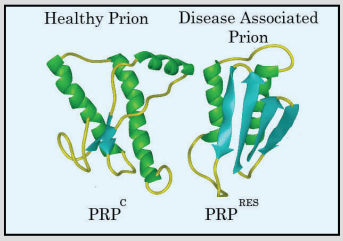
We designed this e-book for wildlife managers and biologist who are responsible for the surveillance of CWD in their state or agency. We chose spatial methods that are popular or

common in the spatial epidemiology literature and evaluated them for their relevance to modeling CWD. Our opinion of the usefulness and relevance of each method is based on the type of field data commonly collected as part of CWD surveillance programs and what we know about CWD biology, ecology, and epidemiology. Specifically, we expected the field data to consist primarily of the infection status of a harvested or culled sample along with its date of collection (not date of infection), location, and demographic status. We evaluated methods in light of the fact that CWD does not appear to spread rapidly through wild populations, relative to more highly contagious viruses, and can be spread directly from animal to animal or indirectly through environmental contamination.

We organized this e-book into 3 chapters by scale and extent for which each spatial epidemiology method was developed or best suited. Specifically, we classify methods into regional, landscape, and fine scales. The first chapter covers methods appropriate to multi-jurisdictional (e.g., multi-state or multi-providence) modeling, which we call "regional" scale. The second chapter covers methods appropriate for statewide or large areas within a state, such as wildlife management unit or county, or for metapopulations, which we call "landscape" scale. The third chapter covers methods appropriate for small areas or local populations, which we call "fine" scale. We know this rubric is somewhat artificial because many methods work at multiple scales. However, when integrating empirical data most methods work best at a particular scale. For example, individual-based models work best at modeling spread within populations, while risk analysis is most useful for summarizing data over larger scales such as a region. We chose to organize the e-book by scale to make it easily accessible to wildlife managers and biologists. Because some methods are applicable at several scales, however, we include a graphic at the beginning of each method that indicates the range of scales for which it applies.

Box I.1. PRION DISEASES

Prions are proteinaceous, infectious disease agents that propagate by converting a normal host protein into an abnormal form. The host protein from which prions can arise is called cellular prion protein (PrP) or PrP^C. PrP^C occurs naturally on the cell surfaces of healthy individuals of all mammalian species studied to date. PrP^C becomes a disease-associated prion when the normal protein folds into an abnormal conformation. This novel PrP conformation (PrP^{RES}) is relatively resistant to proteases, the cellular enzymes that normally break down proteins. PrP^{RES} accumulates during the course of disease in brain and, for some strains and host species, other tissues.



Prion diseases are a family of rare progressive neurodegenerative disorders that affect both humans and animals. Prion diseases are often called transmissible spongiform encephalopathies (TSEs) because, microscopically, the brain shows large vacuoles in neurons associated with prion accumulation. Traditionally, it was thought that all infectious agents responsible for transmissible diseases bore at least some genetic material, either DNA or RNA, in order to propagate in a host. Because prions do not have a nucleic acid genome, the assertion by Stanley Prusiner in 1982 that proteins alone could transmit an infectious disease came as a considerable surprise to the scientific community, and some debate about the true nature of the causative agent continues today. Prion disease transmission is thought to occur because infectious prions are able to induce abnormal folding of normal PrP^C in adjacent cells, allowing the agent to spread within an individual in a crystallization-like process. Of the relatively few known prion diseases, some appear to arise spontaneously, some are heritable, some arise through

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Box I.1. PRION DISEASES
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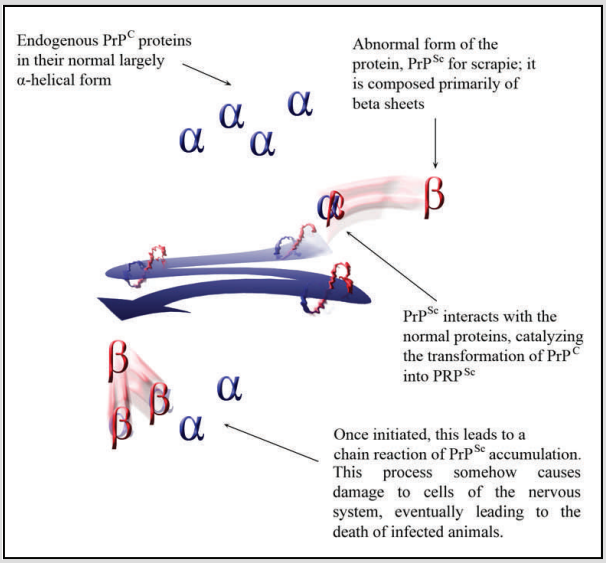
cannibalism, consumption of, or other exposure to infected tissues, and some – including chronic wasting disease (CWD) – are contagious in their natural hosts.



BIOLOGY OF CWD WITHIN AND BETWEEN ANIMALS RELEVANT TO MODELING

There are several aspects of CWD pathogenesis and epidemiology relevant to modeling the disease. First and foremost, CWD is a chronic disease that develops slowly in an individual, taking about 2 years, and sometimes much longer, for infected animals to become clinically symptomatic in captivity (Williams and Miller 2002). Once clinical signs appear, deer in pen-settings typically die in a few weeks to a few months (Williams and Miller 2002). Because the intensity of prion contamination in the environment is likely to be lower for free-ranging populations than captive deer, we speculate that the incubation period may be longer in free-ranging animals. Though, once symptomatic, free-ranging animals may succumb to the disease more quickly due to indirect factors such as increased mortality from predation, hunting by humans, or collision with vehicles. The relationship between disease progression in captive mule deer and free-ranging deer remains unresolved. The time from infection to onset of clinical symptoms is likely to depend upon host genetics (Jewel et al. 2005, Fox et al. 2006, Johnson et al. 2006), infectious dose, and nutritional status or other factors, all of which tend to vary between captive and free-ranging populations. However, because of the extremely high exposure rates in captive studies, which likely result in high dose rates, the rate of disease progression in captive deer may represent the minimum expected in free-ranging deer.

Second, CWD is laterally transmitted through both direct animal-to-animal contact (Miller and Williams 2003) and through indirect environmental contamination pathways (Miller et al. 2004). Prions are highly resistant to environmental conditions that are lethal to other pathogens, as well as to a variety of treatments that typically kill or inactivate conventional infectious agents, such as bacteria or viruses (Brown and Gajdusek 1991). In addition, it appears that some proportion of CWD prions have the ability to remain infectious in the environment for years (Pálsson 1979, Miller et al. 2004).

Besides disease characteristics, demographic patterns of CWD prevalence in mule deer indicate that deer social structure may influence transmission, although the routes of transmission in free-ranging deer are not fully known (Miller et al. 2006). Prevalence of the disease in breeding-age males is 2-4 times higher than in younger males or females (Figure I.2) (Miller et al. 2000, Miller and Conner 2005). Higher prevalence among males, relative to females, may be due to higher exposure risks, higher susceptibility, or lower disease mortality.

At present, higher exposure risk appears to be the most plausible hypothesis. Observations from captive male and female mule deer suggest they are equally susceptible to infection (Williams and Young 1980, Williams and Miller 2002, Miller et al. 2004). No field data exist to suggest diseased males survive for

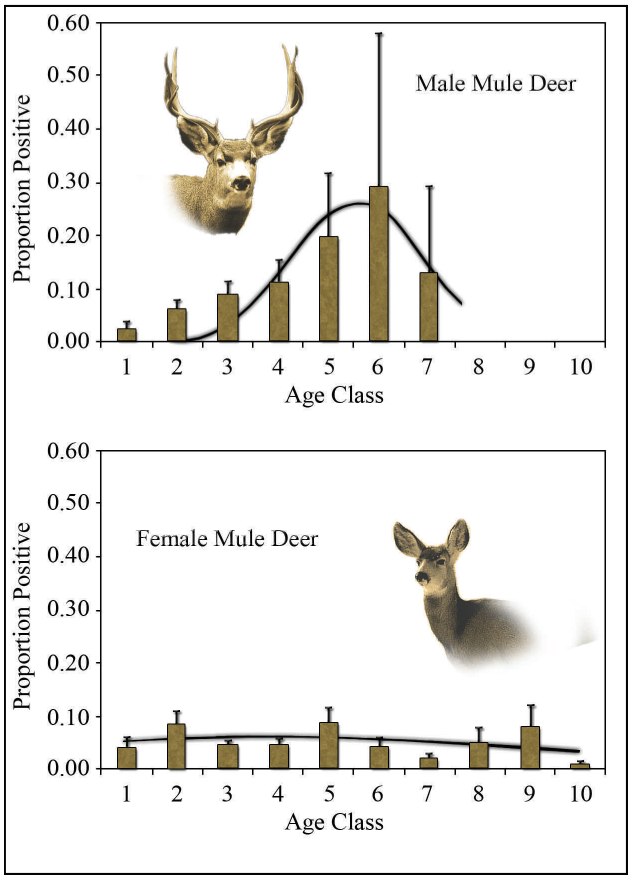
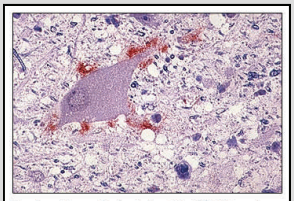


Figure I.2. *Prevalence of CWD by age class for mule deer; based on tooth cementum data collected from surveillance samples in Colorado (1998-2002). Error bars represent 95% confidence intervals. Data from Miller and Conner (2005).*

longer compared to females, and data from pen studies show no difference in survival times of infected males and females (Mike Miller, Colorado Division of Wildlife, unpublished data). Further, male mule deer typically have larger home ranges (Kucera 1978, Kufeld and Bowden 1995) and more social interactions than females (Koutnik 1981), which potentially increases their chance of either direct or indirect contact with infectious CWD prions. Perhaps more importantly, mature male mule deer also practice serial polygyny, where they canvas as many females as possible by sniffing and licking the vulva of females to detect estrus (Estes 1972, Kucera 1978, Geist 1981). Because courtship in mule deer is often protracted (Geist 1981), such contacts likely occur repeatedly during the breeding season. If

Box I.2. PRION PROPAGATION & CHRONIC WASTING DISEASE

CWD-associated prion (PrP^{CWD}) has been identified by use of a special staining process (immunohistochemistry) in neurological tissue of affected cervids, as well as in various tissues of the immune system (collectively called lymphoid tissues), including those associated with the digestive tract (e.g., tonsil, Peyer's patches, and mesenteric lymph nodes). This distribution pattern suggests that PrP^{CWD} may be shed through the alimentary tract.



Brain tissue infected with CWD prions

CWD infection is thought to arise after prions are ingested and subsequently taken up by the tonsils and Peyer's patches. Phagocytic cells at these sites likely engulf the agent, which may then propagate and spread to secondary lymphoid organs where propagation continues. Eventually, PrP^{CWD} enters the nerves of the gastrointestinal tract and ascends to the spinal cord and the brain, where further propagation ensues.

PrP^{CWD} propagation typically occurs much earlier in the disease course in the lymphatic system than in the nervous system. Accumulation of PrP^{CWD} in lymphoid tissues occurs without any appreciable physiological consequence, but accumulation in the central nervous system eventually leads to clinical CWD and death of infected animals. The clinical signs of CWD include behavioral changes, loss of body weight, emaciation, excessive salivation, increased drinking and urination, stumbling, trembling, and depression; behavioral changes include decreased interaction with other animals, listlessness, lowering of the head, blank facial expression, and repetitive walking in set patterns. The diagnosis of CWD is based on examination of the brain or lymphoid tissue for spongiform lesions and/or

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Box I.2. PRION PROPAGATION & CHRONIC WASTING DISEASE
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accumulation of PrP^{CWD} by immunohistochemistry.

Mule deer doe in the mid to late stages of CWD infection.

CWD is transmitted via excreta (Williams and Miller 2002, Miller and Williams 2003, Mathiason et al. 2006), then these behaviors may increase the exposure risk of males. Such behaviors may increase male contact with infectious agent and, accordingly, increase risk of contracting CWD, explaining the observed demographic differences in prevalence.

OBJECTIVES

"All models are wrong, some are useful."
(Box 1979)

Virtually all decisions on natural resource management occur in the face of incomplete data, within a complex and often politically-driven setting, and in systems subject to "surprises". Conceptual and quantitative models offer a means to formally express our understanding of key processes and system dynamics, articulate hypotheses on how we think the system works, and to facilitate communication among diverse audiences. In general, the accuracy of the quantitative model increases with the availability of reliable data. However, even when the data are inadequate, quantitative models can offer a means to examine key relationships and guide management decisions (Starfield and Bleloch 1986).

Disease models can take on an almost infinite variety of mathematical structures and levels of complexity or reality. They may aggregate spatial processes into one or a few simple equations, or explicitly represent spatial heterogeneities in great detail. A model can include random (stochastic) events, or have fixed parameters (deterministic); it can represent a system at a particular point in time (static model), or permit changes over time (dynamic). Table I.1 provides a relatively simple summary of common model types and the characteristics that distinguish each. Differences in model characteristics can overlap, and in these cases it may be a matter of opinion whether a model falls within a category or not. For example, a statistical model composed only of a linear regression is clearly a statistical model (and not a mechanistic model), but the parameters of most mechanistic models can be estimated using a statistical model.

Models of infectious diseases can integrate epidemiological and biological data to give insights into patterns of disease spread (among animals or geographically) and the effect of management interventions. A wide variation in model structures can be used tackle a range of questions and spatial scales. Examples in wildlife and livestock disease systems include analysis of the factors affecting the spread and control of rabies (Smith et al. 2002), foot-and-mouth disease (Ferguson et al. 2001), and bovine tuberculosis (Cross et al. 2004). Here we focus on modeling approaches that are commonly applied to a single population, or to the interaction among populations. However, as modeling sophistication and computing power improve, our ability to use computationally or data intensive approaches at broader scales is rapidly increasing (Ferguson et al. 2005). Similarly, with the increase in computing power, virtually any temporally dynamic model can be extended to incorporate spatial components with the addition of movement rules.

In the sections that follow, we attempt to summarize the utility of different modeling

Model	Explanation
Mathematical	Explicitly represents mechanisms, such as physiological processes, breeding or disease transmission between individuals, or other system-relevant processes. Parameters for process equations generally have an identifiable link to reality. Also called process-based or control model.
Statistical	An equation that describes an observed relationship, but based only on a statistical relationship. Equation parameters usually have no meaningful interpretation, and the domain of inference is usually restricted to very specific areas and conditions. Also called descriptive or phenomenological model.
Dynamic	Explicitly represents change over time.
Static	Describes a system state at a particular point in time.
Non-spatial	Spatial relationships are not explicitly represented , although an area may be implied by representing population density or other area-specific measures. Most models of single populations are non-spatial. Also called spatially homogenous.
Spatially distributed	A non-spatial model applied across an area, but without communications or transfers of energy or materials between spatial units of the model. An example is a point based ecosystem that is applied to a grid of cells, where the model in each cell has unique weather, soils, etc., but seeds or other propaguls are not exchanged between grid cells.
Spatially explicit	A model with communication of attributes between distinct areas that are explicitly represented in the model, and material and energy are exchanged between areas. For example, a disease model where each county is characterized by population density, topography, and disease transmission occurs between counties based on county attributes and disease incidence. Also called spatially heterogeneous.
Stochastic (random)	Random events are included in the model so each instance of the model generates a different result. Model results are typically presented as a distribution or probability of an outcome. Typical random events include weather (temperature, rainfall), variation in contact between infected and susceptible individuals, or random variation in mating or recruitment (especially in small populations). Many consider stochastic models to be more realistic than deterministic models, but they can be much more difficult to evaluate.
Deterministic	Parameters are fixed and each model outcome is exactly the same for a given set of inputs. Common for models composed of differential equations. Deterministic models may have a closed-form (analytical) solution, which can generally simplify analysis.
Analytic	A mathematical model that is solved solely through the use of mathematical arguments and not by numerical approximations or other simulations.
Individual-based	Each individual is explicitly represented in the model. For example, a disease model where the sex, age, disease status, and contacts of each animal in a population are followed for the entire life of each animal.
Spatially explicit	Any model whose behaviors and solutions are obtained by numerical approximations and not by mathematical arguments. Virtually always involves the use of computers.

Table I.1. *Characteristics used to describe or classify models routinely used to model disease dynamics. These terms are not all exclusive, and it may be accurate (and appropriate) to describe a model as having two or more model types. Modified from Haefner (1996).*

approaches to extend our understanding and management of CWD. In particular, we describe and evaluate spatial modeling approaches previously used for wildlife and/or human diseases in the context of CWD. We focus on three spatial scales and present approaches relevant to each. We use spatial scale because for wildlife systems the data available often dictate which scale and resolution are possible. At finer spatial scales, managers and researchers may track known individuals. At broader spatial scales however, this becomes impossible due to logistical and financial constraints. At a state or national scale often the only data available are cross-sectional disease surveys. In the case of CWD, this is primarily done through surveillance of hunter-harvested deer and elk. It is important to note that although data are often limited, the modeling approaches we discuss may be implemented at different spatial scales. For each approach we present the questions addressed, input data required and existing data, model outputs and interpretation, and the use of these results. In addition, we discuss the overall effectiveness of the specific approach to CWD modeling.

We also select a single modeling approach for each scale, which we define as the focal approach. The focal approach is a method that we believe to be applicable to modeling CWD, as well as being a useful tool for identifying management strategies. Note that the epidemiological focus and goals of models vary by scale and these aspects will be discussed later. Using a close facsimile (but not exact to protect unpublished data) of previously obtained CWD surveillance data, we work through the method as an illustration of the strengths and shortcomings of that specific approach. The approaches for each scale are be presented in order, based on our conclusions, from most to least relevant for modeling CWD. At each scale, besides presenting a focal method, we summarize pros and cons of all methods, discuss current data limitations, identify any data gaps for relevant approaches, and describe where future work may be most fruitful.

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